

Review Article

Possibility of non-steroidal treatment in allergic conjunctival diseases

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ABSTRACT

In a recent epidemiological study, 15–20% of the population in Japan was estimated to have allergic conjunctivitis. Allergic conjunctival diseases (ACD) have a wide spectrum of clinical severity and the treatment strategy depends on the severity and duration of the disease. Most cases of the non-proliferative type of ACD, such as seasonal or perennial allergic conjunctivitis, can be treated with topical anti-allergic drugs. Of the ACD, vernal keratoconjunctivitis (VKC) is characterized by typical proliferative lesions, such as giant papillae and severe corneal lesions. Corticosteroid eye drops should be used in combination with anti-allergic eye drops when an anti-allergic drug is insufficient in cases of VKC and atopic keratoconjunctivitis with proliferative lesions. In spite of the high effectiveness of corticosteroid eye drops, they have important side-effects, such as elevation of intraocular pressure leading to glaucoma. Immunosuppressive agents and non-steroidal anti-inflammatory drugs (NSAIDs) are alternative topical agents to corticosteroids. Topically administered immunosuppressive agents, such as ciclosporin and tacrolimus, have antifibroblastic actions by inhibiting remodeling-inducing cells and act as a controller in the treatment of ACD. Non-steroidal anti-inflammatory drug eye drops can be used to inhibit remodeling in ACD because of their excellent anti-inflammatory and antifibroblastic effects, next to corticosteroids and immunosuppressive agents. Substitution of the topical treatment with corticosteroids by these agents in ACD not only spares the use of

corticosteroids and decreases the risk of side-effects, but also brings about a more favorable effect in the long-term control of proliferative-type ACD.

Key words: allergic conjunctival disease, corticosteroid, immunosuppressive agent, non-steroidal anti-inflammatory drug, vernal keratoconjunctivitis.

INTRODUCTION

A previous report indicated that 12.2% of children and 14.8% of adults have a past history of allergic conjunctivitis diagnosed by a physician.¹ Therefore, it is estimated that 15–20% of the population in Japan has allergic conjunctivitis.² Allergic conjunctival diseases (ACD) are one of the most common types of disease seen in ophthalmologic out-patient clinics in Japan and developed countries. The ACD have a wide spectrum of clinical severity and the treatment strategy depends on the severity and duration of the disease. The pathogenesis of these diseases shows an important correlation with systemic allergic diseases, especially atopic dermatitis (AD), which has been increasing in Japan recently, and some types of ACD may also bring about serious visual impairment. The most widely used and basic treatment agents are anti-allergic eye drops, such as disodium cromoglycate (DSCG) and tranilast, which are also called mast cell stabilizers. Corticosteroids have also been considered as the most useful and effective drugs when given locally as eye drops for patients with ACD. However, they have serious side-effects, such as elevation of intraocular pressure (IOP), even with topical instillation as eye drops. We hereafter describe the current therapeutic strategies for ACD according to the severity of the disease and discuss the possibility of non-steroidal treatment in ACD based on recent progress in clinical and immunological studies on ocular allergy.

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CLINICAL FEATURES AND STANDARD OF TREATMENT OF ACD

The Allergic Ocular Diseases Study Group supported by the Japanese Society of Clinical Ophthalmologists has previously proposed definitions and classification of allergic conjunctival diseases, namely, allergic conjunctivitis, atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC) and giant papillary conjunctivitis (GPC).² The former two diseases are non-proliferative and the latter two have proliferative lesions.

Patients with AKC have AD and conjunctival and/or corneal involvement. The corneal and conjunctival lesions in AKC are non-proliferative, showing conjunctival papillae, especially on the upper tarsal conjunctiva (Fig. 1), or superficial punctate keratopathy, in contrast with that in VKC, which exhibits proliferative lesions such as giant papillae or corneal plaques.³ The major symptoms of allergic ocular disease are itching, tearing and foreign body sensation, but, in contrast with viral conjunctivitis, ocular discharge is rare. Dry eye caused by a decrease of conjunctival goblet cells is sometimes seen in ocular allergy. Follicles and papillae are the most typical findings in the conjunctiva. Superficial punctate keratitis is found in some cases. Giant papillary conjunctivitis, in which giant papillae >1.0 mm in size are found, is caused by extended wearing of soft contact lenses, stimulation by ocular prostheses or surgical sutures in the upper tarsal conjunctiva.

Vernal keratoconjunctivitis is diagnosed by slit lamp examination showing typical cobblestone excrescences (giant papillary conjunctivitis of the upper palpebral conjunctiva >1 mm in size; Fig. 2), perilimbal gelatinous

change and severe corneal lesions, such as plaques or ulcers (Fig. 3). These patients have very severe clinical symptoms, more marked than those in allergic conjunctivitis, including positivity for serum antigen-specific IgE. Vernal keratoconjunctivitis is often seen in young men with a history of AD.⁴ It has been reported that cellular immunologic reactions play an important role in the development of the severe ocular lesions that are often found in patients with VKC.

Results of recent studies indicate a predominance of T helper (Th) 2 activity in ocular allergy.⁵ The serum level of IgE is significantly increased in AD patients with ocular complications compared with AD patients without ocular complications, and the positive rates of IgE-RAST (radioallergosorbent assay) for rice and wheat are significantly higher in ocular-type AD than in non-ocular-type AD.⁶

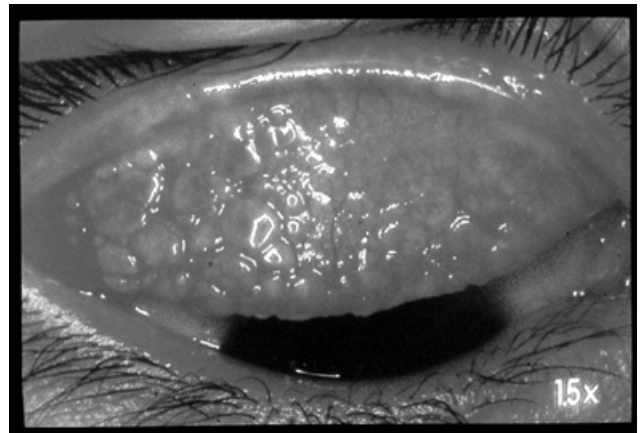


Fig. 2 Conjunctival finding of vernal keratoconjunctivitis. Typical cobblestone excrescences are shown in a patient with atopic dermatitis.

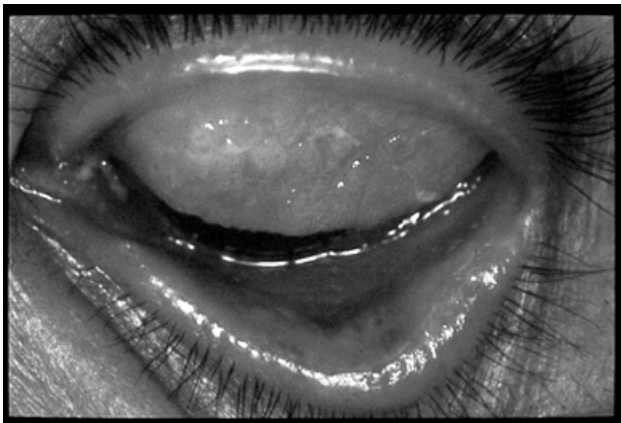


Fig. 1 Conjunctival lesion of atopic keratoconjunctivitis. Slight conjunctival hyperemia and pigmentation are observed.

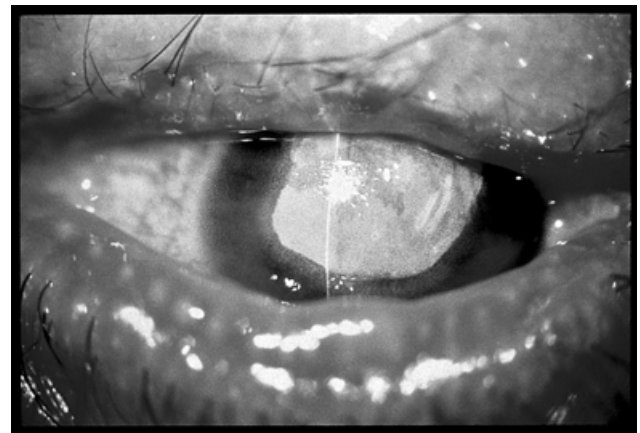


Fig. 3 Corneal involvement of vernal keratoconjunctivitis. A corneal ulcer complicated by a corneal plaque is shown.

These results suggest that ocular-type AD belongs to the most severe end of the spectrum of AD and that some food antigens may contribute to the pathogenesis of severe AD resulting in ocular complications.

Most cases of allergic conjunctivitis can be controlled by local (eye drops) anti-allergic drugs (Table 1). Corticosteroid eye drops should be used in combination with anti-allergic eye drops only when an anti-allergic drug is insufficient. Anti-allergic eye drops are divided into two types: (i) those that act solely as an inhibitor of chemical mediator release (pemirolast potassium, cromoglycate sodium, tranilast and amlexanox); and (ii) those that inhibit the release of both chemical mediators and histamine (ketotifen fumarate).

Anti-allergic eye drops are used in recurrent cases of pollen-induced conjunctivitis as a prophylactic treatment 2 weeks prior to the pollen season. Immunotherapy is the sole etiotropic treatment for ocular allergy and may be tried for juvenile cases in which the causative allergens are known.

Emedastine and azelastine (chemical mediator inhibitor and histamine antagonist), levocabastine (specific histamine H₁ receptor antagonist), apafant (inhibitor of platelet-activating factor) and ciclosporin (immunosuppressive agent) are under clinical trial for ACD in Japan. An inhibitor of cytokine synthesis (suplatast tosilate⁷), an inhibitor of thromboxane (TX) A₂ synthesis (ozagrel sodium⁸), a TXA₂ receptor antagonist (seratrodast⁹) and a leukotriene receptor antagonist (pranlukast¹⁰) are under investigation as ocular topical treatments. In the near future, more types of eye drop drugs will be available for ACD, including the above-mentioned agents.

In contrast, however, the above-mentioned therapeutic measures are often ineffective in VKC with proliferative lesions. Corticosteroid eye drops are necessary to treat

these patients, because allergic proliferative lesions, such as giant papillae and limbal infiltrative changes, are considered to represent tissue remodeling due to recurrent epithelial inflammation and imperfect tissue repair.¹¹ For the long-term control of allergic inflammation including ACD, topical instillation of corticosteroids is essential. However, corticosteroids have several unwanted effects, as described later, and the lack of effective treatment to spare the use of corticosteroids has been considered an important clinical problem.

Removal of causative foreign bodies, such as contact lenses, ocular prostheses or surgical sutures, should be the primary treatment in GPC. If contact lens wear cannot be stopped, a gas-permeable lens or non-ionic low-hydrous soft lens should be used. In these cases, anti-allergic drugs may be given topically, but corticosteroid eye drops should not be used. Because parasites may, rarely, cause GPC, close observation of the tarsal conjunctiva is necessary when an ordinary causative material is not found. Cleaning of the skin with 50% baby shampoo and moistening with white petrolatum is effective for eczematous eyelid involvement in AD patients.

SUBSTITUTIONAL TREATMENT MEASURES TO SPARE THE USE OF CORTICOSTEROIDS

In spite of the high effectiveness of corticosteroid eye drops in the treatment of ACD, they have important side-effects, such as elevation of IOP leading to steroidal glaucoma, induction of infectious keratitis or conjunctivitis and prolonged epithelial defect. The most important and serious side-effect is ocular hypertension, which is thought to be genetically determined,¹² and such patients are termed 'steroid responders'. The use of topical corticosteroids is contraindicated in these patients and if they have proliferative ocular lesions in

Table 1 Pharmacological features of anti-allergic eye drops

Drugs	Histamine antagonist	Stabilization of mast cells	Specific feature	Other characteristic
Cromoglycate sodium	—	○	TGFβ antagonist	Twice a day instillation
Tranilast	—	○		
Amlexanox	—	○		
Ibudilast	—	○		
Tazanolast	—	○		
Pemirolast potassium	—	○		
Ketotifen fumarate	○	○		
Levocabastine	○	—	Specific histamine H ₁ receptor antagonist	

TGFβ, Transforming growth factor β.

VKC or AKC, treatment without corticosteroids is very difficult. To decrease the topical use of corticosteroids, there are several alternative routes for corticosteroids as follows. Frequent instillation or subconjunctival injection of corticosteroid with 1.0% lidocaine hydrochloride may be effective for corneal complications and giant papillae in VKC. Sub-bulbar conjunctival water-soluble steroid may be injected for the treatment of limbal proliferative lesions of VKC. Triamcinolone acetonide, which diffuses slowly into tissue, is also widely used clinically for long-term control in patients with VKC. Oral administration of prednisolone or methyl prednisolone at 5–20 mg every other day may be effective for serious cases, because these drugs have a short half-life in the blood. Prolonged systemic administration of corticosteroids with a long half-life, such as betamethasone and dexamethasone, may cause suppression of adrenocortical function or inhibition of methaphyseal growth. These routes of systemic or local administration of corticosteroids are effective and decrease the risk of IOP elevation and other side-effects specific to corticosteroid eye drops.

Other types of drugs can be used topically to support or substitute for corticosteroids, namely immunosuppressive agents and non-steroidal anti-inflammatory drugs (NSAIDs). The immunosuppressive agents ciclosporin and tacrolimus are under clinical trial in Japan for the treatment of VKC and chronic-type ACD. Ciclosporin eye drops are reported to have a similar effect to corticosteroids on proliferative lesions in VKC.¹³ The mechanism of action of ciclosporin in the treatment of VKC is not only suppression of cellular immunity, but also a suppressive effect on non-immunological cells, such as vascular endothelial cells, corneal stromal cells and fibroblasts.¹⁴ Based on their pharmacological properties, immunosuppressive agents lack an immediate effect and anti-allergic activity and have less anti-inflammatory activity compared with corticosteroids, but have a sufficient anti-fibroblastic action by inhibiting remodeling-inducing cells, such as vascular endothelial cells, fibroblasts and mast cells. Thus, topically administered immunosuppressive agents act as controllers in the treatment of ACD.

Non-steroidal anti-inflammatory drug eye drops have been recognized recently as one of the treatment measures in ACD, with a similar effect to that of anti-allergic eye drops (Table 2).^{15–17} Of the NSAIDs, pranoprofen, diclofenac sodium and bromfenac sodium are currently commercially available as eye drops in Japan. Although ketorolac is widely used in patients with ACD in Europe and has been shown to have satisfactory efficacy,¹⁷ it is

Table 2 Non-steroidal anti-inflammatory drug eye drops for allergic conjunctival diseases

Drugs	Specific characteristics
Pranoprofen	
Diclofenac sodium	
Bromfenac sodium	Twice a day instillation
Indomethacin	0.5% oily solution

not authorized for topical use in Japan. Non-steroidal anti-inflammatory drugs decrease hyper-reactivity of inflammatory cells, such as mast cells and lymphocytes, during re-epithelialization after keratoconjunctival inflammation and lead to suppression of fibroblastic and vascular endothelial cell activity, as well as having anti-allergic activity comparable with that of anti-allergic eye drops.^{18,19} Therefore, NSAID eye drops can be used a controller against remodeling in ACD owing to their excellent anti-inflammatory and antifibroblastic effects, next to corticosteroids and immunosuppressive agents. Based on these interesting pharmacological features of NSAIDs in the topical treatment of ACD, combined long-term local application of NSAID eye drops with corticosteroid and anti-allergic eye drops has potential in the treatment and control of VKC. However, NSAID eye drops may induce corneal complications and sometimes induce anaphylactic reactions owing to their aspirin-like properties. Non-steroidal anti-inflammatory drug eye drop-induced asthma attacks have been reported in patients with aspirin sensitivity.^{20,21} The NSAID eye drops should not be given to patients with asthma and aspirin sensitivity unless the patient is known to tolerate NSAIDs without trouble.

CONCLUSIONS

Immunologic and allergologic mechanisms are involved in the development of ocular allergic diseases and they have an important relationship with the treatment of ACD. Substitutional topical treatment measures for ACD to corticosteroids by immunosuppressive agents and NSAIDs not only spare the use of corticosteroids and decrease the risk of IOP elevation, but also bring about a more favorable effect in the long-term inhibition of proliferative lesions in VKC. Clinical and basic research in ocular allergy is expected to develop drugs that can be used more safely and efficiently for such patients and improve the quality of life of patients with ACD.

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